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7/12/82

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File PCBs

DMEH CENTRAL FILES

Rebuttal to Health and Environmental Review Division's Review of Studies On the Health Effects of PCBs.

Introduction

data as such not being debated.

note interpretations of data and judgements relative to human significance are not same as experimental animal data.

different interpretations should highlight need for weighing possible conclusions before adopting one

different interp. show case not clearcut

by

Robert C. James, Ph.D.
Morris F. Cranmer, Ph.D.
and
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MONS 212696

General Comments

The review performed by the Health and Environmental Review Division (HERD) of the Environmental Protection Agency (EPA) regarding the summary of the health effects of PCBs written by Ecology and Environment (E & E) on behalf of the Chemical Manufacturers Association (CMA) suggests that the HERD review group misunderstood the intent of and contents of the document.

The summary document reviewed the pertinent literature regarding the human health effects and animal or in vitro toxicity studies as a means of estimating the human health risks to be expected from the current human environmental exposures to PCBs. The HERD group review constantly focuses on potential hazards, generally based upon animal data showing effects that may occur at high doses in a specific animal species without addressing the real problem, i.e., what are the likely consequences in humans enviromentally exposed to small amounts of PCBs.

The HERD group in several instances refuses to accept the idea that chemicals may increase tumors in animals via an initiation or promotion process, and that these processess differ greatly in mechanism and in their application for estimating human risk. The authors do not understand that HERD reviewers dismissal of current principles and concepts of chemical-induced cancer; for well known scientists within the EPA, FDA, and the majority of the scientific community at large consistently use and have accepted these principles and concepts. Failure to consider new information in the form of principles and concepts is not scientifically supportable.

The following paragraphs contain adequate and appropriate responses to each question raised by the HERD group. Our previous position concerning the potential health effects of PCBs expected from environmental exposures stands and has been recently strengthened by a similar evaluation coming from a separate group of distinguished toxicologists whose conclusions were similar to ours. Furthermore, the HERD reviewers questions likewise have strengthened our position by asking us to cite others who feel PCBs have promoting activity.

Since the authors and the HERD review group are in disagreement regarding the risk posed by PCBs, the authors wish to state a major concern they have for the risk from PCBs proposed by the EPA. A short perusal of the federal register, Volume 45, pages 79318-79379, indicates that the EPA has come to a most distressing and indefensible conclusion. In these pages, the EPA has proposed, based upon human health, an acceptable water concentration for PCBs which is some 8,000 times lower than that proposed for benzene, 25,00 times? lower than that established for vinyl chloride, and of the same magnitude but lower than those levels proposed for benzidine, polyaromatic hydrocarbons and alkylnitrosamines. Even taking into consideration that 99% of the consumption of PCBs was projected to come from fish, EPA has made a serious error by implying that the risk from PCBs is greater than or equivalent to the risk posed by chemicals known to be human carcinogens or chemicals representing reactive, potent, mutagenic/carcinogenic substances. We find this a conclusion that cannot be based upon consistent, objective toxicological principle or risk analysis methods. We wish the HERD group would objectively and scientifically explain this stand. Since we feel they cannot, we must once again conclude that the risk proposed for PCBs represent an "over zealous and inappropriate use of mathematical models and assumptions without comparing these results to reality."

Specific Comments

1. The EPA-HERD Reviewers state, "These documents are somewhat unobjectively written with unscientific discussions such as:

This general statement by the EPA HERD reviewers is incorrect in the authors opinion. The reports for the CMA and NEGA were intentionally written in a manner to promote an understanding of the authors' conclusions by the lay reader. The scientist/researcher has access to original articles and can draw their own conclusions. The authors see no need for the EPA to interpret this approach as an unscientific or unobjective. The authors mentioned both the positive and negative data, and attempted to explain to the reader the basis for their decisions and interpretation. The authors cited and referenced both the NIOSH and EPA reports and their interpretations of the data. While the authors did not pursue in depth EPA's line of reasoning it should be emphasized the previous EPA report did not propose alternate interpretations such as the authors report emphasizes. The authors insist that focusing on one's own conclusions does not represent a lack of objectivity if other viewpoints previously developed are cited. On the contrary, if the EPA suggests that focusing on ones own viewpoint is unobjective they should then follow their own advice.

The authors are confused as to EPA's position with respect to the statements (a), (c), and (d) since they are true statements. Toxicology is a science which often requires comparative decisions, (species to species, compound to compound, dose to dose) to gain a fair perspective of any problem. Comparisons are particularly pertinent in discussing risk if risk is defined as the probability of occurrence. It is not clear as to why EPA objects to comparisons of

PCB toxicology with that of common chemicals. Such comparisons must be made or the lay person may be easily mislead into thinking that only very dangerous chemicals can produce positive results in toxicological tests. The intent of the comparisons ~~are~~ to demonstrate to the lay person (the toxicologist is already knowledgeable) that a toxic effect in animals does not mean that all animals or all human exposures will result in a similar response. A detailed discussion of the specific EPA-HERD comments follows.

1a. The EPA reviewers characterized as unobjectively written with unscientific discussion the statement, "However, the overzealous use of mathematical models and the assumptions made by the EPA without comparing these results to reality are easily demonstrated".

This statement was made in context and to make a simple point. When human data are available those data should take precedence over animal data and conservative assumptions which regulators may justifiably argue when animal and human data are not available. A careful reading of the discussion in the authors opinion justifies the wording chosen. The original text follows with critical points highlighted. Following the text is a concluding discussion further documenting the lack of merit of EPA grievances.

"Conclusions About the Application of Linear Extrapolation and the Equivalent Nonthreshold Models to Risk Analysis of PCBs

We will establish our thesis when we thoroughly analyze the risk analysis offered by Crump. When referring to his modeling efforts, Crump states, "The expected numbers of extra cases of hepatocellular carcinomas per year resulting

from a nationwide exposure at a dietary level detected in the 1976 Total Diet Study (3.3 µg/day) would range between 220,000/(288,000 x 70) = 11.1 cases/year and 220,000,000/(764,000 x 70) = 4.1 cases/year."

Crump misleads the reader by suggesting that the mathematical model used to generate these numbers brings logic to the effort. For example, if one simply takes the ratio of animals with and without liver tumors at 100 ppm in the Kimbrough study, divides by the estimated human exposure (1 ppb), then multiplies by the size of the human population in the United States (220 million), and finally divides by the human lifespan of 70 years, one gets the same answer as Crump:

this doesn't agree with this → 100

26 tumors/184 animals 1 ppb PCB/200 ppm PCB/70 years = 4.3 cancers/year.

Crump's analysis of risk to infants is markedly overstated. A rat consumes approximately 10% of its body weight per day. Feed with 100 ppm PCB equals a consumption of 100 mg/kg. Therefore, a rat consumes the equivalent of 10 mg PCB/kg/day. If the human milk sample was 2% fat, then the whole milk would contain 2% of the 4 ppm Crump considered, or .08 ppm. A liter a milk would contain .08 mg of PCB. A child weighing 6 kg would have to consume 750 liters of milk a day to equal the exposure of the rats. If the child truly only consumes 1.5 liters a day, then there is a 500-fold difference in exposure rate between rat and baby.

If the baby is exposed, as suggested by Crump, for only 1/140 of its lifespan, this has to be considered. The 500-fold difference times the 1/140 of the lifespan is equal to a 70,000 exposure differential. The linear risk as calculated

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by Crump's technique would be 2/1,000,000, not the 1/4,800 reported by Crump.

If we approach the problem another way, we obtain other interesting comparisons. The PCB dose to high exposure women averaged 1.7 µg/kg/day. A lactating female maintaining her weight would then have 1.7 µg x 50 kg, or 85 µg/day of PCB, available for transfer to the baby. If the baby weighs 6 kg, the dose is 14 µg/kg/day. This, when compared to the 10 mg/kg/day dose to the rats, yields an exposure ratio differential of 700 times. The exposure period of 1/140 times the exposure ratio yields a total exposure risk of 98,000 times less for the humans than the rat. The linear risk as calculated by Crump's technique would be 1.4×10^{-4}, not the 1/4,800 reported by Crump.

If one insists on linear extrapolation, what are the relative risks? Let us assign an average exposure resulting in 500 ppb blood level to capacitor workers, 70 ppb to the heavy fish eaters in Michigan, and 20 ppm to the general Michigan population. Let us assign an exposure of 12 µg/kg/day to the capacitor, 1.7 µg/kg/day to the fish eaters, and .5 µg/kg/day to the general population. These estimates were taken from the documents of Crump and the EPA water quality criteria for PCBs.

The rats in the Kimbrough study were exposed to 10,000 µg/kg/day. Therefore, the ratio of exposure between rats and man is:

Capacitor worker/rat = .0012

Fish eater/rat = .00017

General population/rat = .00005

The chances of dying from liver cancer can be expressed in several ways. For ex-

ample, 816.3/100,000 Americans die each year from all causes. The incidence of liver cancer disease is 3/100,000. This translates to a .37% chance that the cancer seen will be liver cancer. Expressed another way, there will be about 2,000,000 deaths in 1981 and 9,400 are estimated to be from liver cancer. Therefore, 9,400/2,000,000 equals a .47% chance that the registered death will result from liver cancer. This estimate will be rounded off to a .5% chance for the purposes of our discussion.

If the risk were linear (and the risk to humans is the same as in rats, or .14), then the risk in man would be .00017 for capacitor workers, .00024 for fish eaters, and .000007 for the general population. Expressed another way, the risk to humans for liver cancer would increase to:

Capacitor worker	.005 + .00517 = .01017
Fish eater	.005 + .000024 = .005024
General population	.005 + .000007 = .005007

Thus, the cancer mortality data suggest that there is only a slight possibility that the actual risk for capacitor workers would be higher; however, the data are far from conclusive. It is also obvious that it would be impossible to determine epidemiologically the tiny increases expected to occur either in the fish-eating population or in the general population.

Approaching the problem from a different viewpoint, let us suppose that our risk analysis should be conducted on a relative risk basis. If the relative risk to rats at 100 ppm is 26, and the same exposure ratios between rat and man hold, then the risks are as follows:

Capacitor worker .005 + .0012 x 26 = .0362 (724% background)

Fish eater	.005 + .00017 x 26 = .0094 (188% background)
General population	.005 + .00005 x 26 = .00552 (110% background)

Again, this hypothesis cannot be rejected at the lower exposures because it is not possible to anlayze it on the basis of information available. However, the data on capacitor workers aid in the evaluation of this hypothesis since the highly exposed individuals would demonstrate an incidence which is seven times the background incidence. Since the NIOSH study suggests that the conclusion cannot be true, the risk to man is not the same and is less than that risk proposed based upon the one positive study for rats.

How Did EPA Analyze the Data?

The preceding discussions of human exposure makes clear the fact that a high percentage of the United States population has been and is exposed to low levels of PCBs in food, water, and air. Those groups at particular risk from PCB exposure include industrial workers exposed in the workplace and individuals consuming large amounts of contaminated fish, such as some sport fishermen (42 FR 17487).

An assessment of carcinogenic risk was made by EPA performing extrapolation from animal data using a linearized multistage (non-threshold) model. The extrapolation used was reported to take into account the bioaccumulation of PCBs in fish and shellfish. It is assumed that an average of 2 liters/day of water are consumed along with 6.5 g of fish taken from that water source. Exposures from other food sources, air, or occupational exposure are not included in the criterion level derived by this model.

Among the studies reviewed by EPA, only one was considered suitable for use in the cancer risk assessment. EPA made the remarkable statement that, "Of the rat studies, the only one involving long-term exposure and adequate numbers of animals is the study of Sherman rats by Kimbrough et al. (1975)." EPA goes on to state, "Because there is no recognized safe concentration for a human carcinogen, the recommended concentration of PCBs in water for maximum protection of human health is zero." Since attaining a zero concentration level may be infeasible in some cases, and in order to assist the agency and states in the possible future development of water quality regulations, the concentration of PCBs corresponding to several incremental lifetime cancer risk levels have been estimated. A cancer risk level provides an estimate of the additional incidence of cancer that may be expected in an exposed population. A risk of 10^{-5}, for example, indicates a probability of one additional case of cancer for every 100,000 people exposed, a risk of 10^{-6} indicates one additional case of cancer for every million people exposed, and so forth.

In the Federal Register Notice of Availability of Draft Ambient Water Quality Criteria, EPA stated that it is considering setting criteria at an interim target risk levels of 10^{-5}, 10^{-6}, and 10^{-7}, as shown in Table 3.5.

If 80 ng/day is the EPA's estimate, how does it compare with other EPA statements and those results gathered in the NIOSH and FDA studies? Even when one makes all the conservative assumptions utilized in official PCB cancer risk estimations, one arrives at answers which are so low as to escape our capability of detecting a positive effect via epidemiology. Therefore, one must conclude that mathematical risk estimation, even for the occupationally exposed, yields estimates which are vanishingly small. However, the overzealous use of math-

ematical models and the assumptions made by the EPA without comparing thes results to reality are easily demonstrated. EPA states in the Federal Register Notice of Availability of Draft Ambient Water Quality Criteria that the following risk to cancer from PCBs exists, 10^{-5} cancer risk = 80 ng PCB/day.

Table 3.6 summarizes known human exposures to the risks calculated by an extrapolation of the values.

Using estimated performed on preceding pages calculated from actual cancer rates in the United States, 9,400/2,000,000 equals a .47% chance of dying from liver cancer. This estimate will be rounded off to a .5% chance for the purposes of discussion. Using these comparisons, it can be seen from the table above that if the EPA estimates are correct then 10% of the liver cancer in the United States would be due to PCB exposure; the Michigan control population would expect a 100% increase in liver cancer incidence, the Michigan fish eaters would have a 3-fold increase, the average capacitor work would have a 10% incidence of liver cancer or a 20-fold increase, and the highly exposed capacitor worker would have a 25% incidence of liver cancer or a 50-fold increase. No human evidence supports any of these sstimates. On the contrary, it is obvious that the EPA standard is from 10 to 100 times more severe than can be justified on the basis of human experience, and from 10- to 20-fold more severe than can be excluded on the basis of human experience. As our data bases grow, it is likely that the standard will be found to be at least another order of magnitude too severe.

In summary, the rationale that was used by Crump and Masterman in establishing the PCB cancer risk was based on a genotoxic theory of carcinognesis and

was compiled from a series of ultra-conservative assumptions, which are not valid in light of much evidence to the contrary. These assumptions ignored the fact that PCBs are not genotoxic; utilized only the positive data and ignored the negative data; applied constraints to mathematical models which transformed them to equivalent of linear extrapolation; ignored all other competing causes of death; equated cancer risk in the last moment of life with the risk of a newborn; and exaggerated exposures, for example: assumed that mother's milk was 100% fat, equated all PCBs' toxicities as the most toxic results observed for any PCB, and ignored the reversibility of PCBs' effects and the marked improvement in human exposure levels that has occured in the last five years. reduction?

Furthermore, using a mathematical model to extrapolate the risk at lower doses does not increase the reliability of animal data. The most important question still remains: "Do the animal data reflect the human situation and response?" With the addition of the NIOSH study on capacitor workers to the PCB literature it can be demonstrated that the risks estimated using Crump's model are unrealistically conservative by several orders of magnitude. In a practical sense, a substantial number of people have been chronically exposed to higher levels of PCBs for a longer period of time than that which occurs for the general population. Since no adverse health effects were causally demonstrated in this population, no measurable adverse effects would be expected for the general population.

Table 3-5

EPA INTERIM TARGET RISK LEVELS

Exposure Assumptions	Risk Levels and Corresponsding Criteria[1]		
	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 6.5 g fish and shellfish only[2]	0.0079 ng/l	0.079 ng/l	0.79 ng/l (160 ng/day)
Consumptions of fish and shellfish only	.0079 ng/l	0.079 ng/l	0.79 ng/l (160 ng/day)

[1]Calculated by applying a linearized multistage model as discussed in the Human Health Appendices to the October 1980 Federal Register notice which announced the availability of this document. Since the extrapolation model is linear at low doses, the additional lifetime risk is directly proportional to the water concentration. Therefore, water concentrations shown in the table above vary by factors of 10, 100, 1,000, and so forth.

[2]Approximately 99 percent of the PCB exposure results from the consumption of aquatic organisms which exhibit an average bioconcentration potential of 31,200-fold. The remaining 1 percent of PCB exposure results from the drinking water itself.

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Table 3-6

EXTRAPOLATIONS OF EPA CALCULATED RISK LEVELS TO A HIGHER LEVEL OF HUMAN EXPOSURE

Group	Blood Exposure		EPA Extrapolated Risk
	Blood	Exposure	
Highly exposed capacitor workers	≥1,000 ppb	2 mg PCB/day	25%
Average capacitor worker	500 ppb	.84 mg PCB/day	10%
Michigan fish eater	70 ppb	.12 mg PCB/day	1.4%
Michigan control population	20 ppb	.035 mg PCB/day	.5%
General population	2 ppb	.0035 mg PCB/day	.05%

Besides the preceeding arguments which were previously stated, there is one additional comparison that easily demonstrates that the EPA's calculation for risk is inaccurate. The model predicting the cancer risk from PCBs based on the data from the Kimbrough et al. study (1) used by EPA is linear in the dosage range calculated for the acceptable risks of 10^{-5}, 10^{-6}, and 10^{-7}. Linear extrapolation provides an overestimation of the actual dose required for a high incidence of cancer (see Figure 1). This is easily demonstrated by performing upward linear extrapolation. For example, if 10^{-5} risk is equal to 160 ng/day, a 100% risk is calculated as 10^5 x 160 ng/day and equals 16 mg/day. Restated, a 16 mg/day-exposure to PCBs is calculated to predict a cancer incidence of 100% if the assumptions made to calculate the low exposure risk are correct. The authors offer additional arguments that maintenance of such an attitude is to obfuscate.

Prior to the PCB ban, the Occupational Safety and Health Administration's (OSHA) limit for occupational exposure to PCBs was 0.5 mg/m^3 for Aroclor 1254 and 1.0 mg/m^3 for Arclor 1242 and other lower chlorinated biphenyls. The average volume of air inhaled per workday is approximately 10 m^3, and the allowable workday intake of PCBs approximated 5 to 10 mg. The authors grant that not every worker was exposed daily to these levels, however, numerous reports such as Ouw et al. (2) or Brown and Jones (3), illustrate that in several instances exposures were higher; therefore, the authors have assumed these daily exposure approximates are reasonable. Since the study of Brown and Jones (3) did not find a statistically significant increase in cancer, and since a 10-100% incidence of cancer or a 40-400% increase in the cancer rate could not escape detection in the studied groups of occupationally exposed persons, one must again conclude that the EPA cancer risk extrapolated from the data of Kimbrough et al., for low dose ex-

posure is in error by two to three orders of magnitude or perhaps even greater (see figure 1).

The authors are once again forced to conclude that since the EPA calculated level of risk cannot possibly agree with the human experience and the EPA approach is indeed an overzealous use of mathematical models since there was no attempt to compare the EPAs calculated results to the real life situation.

1b. The EPA-HERD reviewers state, "The report by the New England Gas Association begins "The discovery of small amounts of PCBs, the use of which has been banned by the EPA, in natural gas transmission lines is neither unexpected nor cause for public alarm.""

This statement is an excerpt supplied by NEGA and not a statement of the authors of the report.

1c. The EPA-HERD reviewers state, "Later in discussing acute PCB toxicity the report states: "Short term effects of moderate doses in animals are minimal. The toxicity is comparable to that expected from such substances considered relatively safe such as table salt, alcohol or caffiene.""

The acute toxicity as measured by the LD_{50} for PCBs is comparable to that for table salt or alcohol. This is a legitimate comparison of the animal lethality (4). This comparison was offered to help lay readers attain a balanced perspective as to whether or not the LD_{50} for PCBs should be considered a high or low value.

troublesome to the regulator

a true statement (4). In fact, the spec

effects for common substances such as aspirin,

normones is greater than for PCBs.

and hormone

2. The EPA-HERD reviewers state, 'The "Summary of the H

PCBs" tends to misguide the reader as to what the actual articles

overall tone of the Summary is a refutation of the technical present

exaggeration of the "negative" arguments presented in the six review a

The CMA document does not misguide the reader, on page 1 of the executive su

ry is it clearly stated that after a review of the readily available and signi

icant studies of the effects of PCBs that it was the authors independent

professional opinion that environmental exposures to PCBs do not pose a signif-

icant health risk. It should therefore be obvious to the reader that the summa-

ry report will differ vastly from the EPAs report. The authors addressed the

importance of negative studies as well as positive studies. The authors do not

consider a subsequent discussion of the factors which influenced their ultimate

decision to be an "exaggeration of the negative data" nor should the EPA. An-

other independent review of PCBs has been developed subsequent to the authors

report. This report reaches substantially the same conclusion that we came to.

In order to emphasize this point the executive summary of this report is pre-

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DRAFT

Potential Health Effects in the Human From Exposure to Polychlorinated Biphenyls (PCBs) and Related Impurities

Prepared by:

Drill, Friess, Hays, Loomis & Shaffer, Inc.

EXECUTIVE SUMMARY

"The present study on the potential health effects in human populations from exposure to commercial polychlorinated biphenyl (PCB) mixtures under occupational or other environmental conditions was conducted by a team of specialists in the medical, toxicological and epidemiological sciences designated as the Category I team. Draft material for the study report was reviewed by a second group of specialists designated as the Category II team, and other scientists, leading to comments and suggestions for improvement which were incorporated into the draft report. The available body of scientific literature on health effects of PCBs in humans and in test animal systems was reviewed and analyzed with emphasis on the relationships linking exposure, dosage to the biological target, and occurrence of specific health effects in the animal or human. Both the toxicological and epidemiological data from acute and chronic animal and human exposures were considered in generating assessments of the probability of occurrence of any specific health effect in humans. The results of these assessments are summarized below, separately itemized under each major health effect. It should be noted that each assessment applies to the potential for development of that effect under the type and level of human exposures actually encountered in the U.S. during the past decades, with the most intensive integrated exposures having occurred in manufacturing operations that were terminated in this country in 1977.

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Separate consideration was devoted to the Yusho episode recognizing the spe character of the human exposures to high concentrations of mixtures of PCBs their thermal degradation products, polychlorinated dibenzofurans (PCDFs) polychlorinated quaterphenyls (PCQs). Several conclusions reached by the Cat gory I team are of importance: (a) it is impossible to stipulate whether any the health effects observed is casually related to PCB exposure, since the othe halogenated compounds are also biologically active; (b) the dosage patterns experienced by Yusho patients and U.S. industrial workers (PCB-exposed) are not at all comparable; the latter group experienced low level, long time period exposures primarily via inhalation and skin contact, with only minimal oral ingestion; (c) the similar health effects seen in Yusho patients from the Japanese and Taiwanese episodes of exposure to contaminated cooking oils point to the same type of toxic mixtures resulting from thermal heat exchanger action in the two events; (d) because of points (a)-(c) above, and the fact that at least the PCDFs in the Yusho oils are potentially more toxic than the PCBs on the basis of animal data, it is not possible to extrapolate the Yusho experience to prediction of acute and sub-chronic effects of commerical PCB mixtures in the human; (e) finally, with respect to predictions of human carcinogenesis from the Yusho type of exposure the data are so incomplete that conclusions regarding any types and amounts of excess cancers attributable to those exposures have to await further definitive study.

Body Burdens, Metabolism, and Kinetics

Some general observations derive from consideration of the data on the storage,

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distribution, metabolism and excretion of commercial PCB mixtures (with associated impurities such as the PCDFs) in mammalian systems. The dynamics of the pathways by which these processes occur in test animal models have been explored intensively and have been fairly well worked out. The variability of PCB effects with species of test animal model model has been investigated for a number of important effects, and some general structure vs. activity rules have emerged from these studies. There thus exists a conceptual framework, but not experimental data, for describing such phenomena in humans. Furthermore, important data on the biochemical interactions of PCBs, PCDFs and metabolites with tissues have been obtained that bear directly on interpretation of toxic effects in these tissues.

General Toxicity

From acute, subchronic and chronic studies of PCB effects in test animal models, a general summary of health effects encountered includes: (a) a low order of acute toxicity; (b) skin lesions; (c) effects on liver tissue that are generally reversible at lower doses but that trend toward irreversibility with increased dosing; (d) effects on the gastric mucosa; (e) effects on the menstrual cycle and on reproduction; (f) porphyria; (g) effects on the kidney; and (h) miscellaneous changes including hematologic alterations, thymic atrophy and lymphatic changes.

There is a considerable range of species susceptibility to biological activity of the PCBs, with one representative comparison of order of decreasing activity being mink, monkey, rat. It is concluded that there is no basis for determining which species most accurately serves as a model for prediction of general sub-

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chronic/chronic toxicity in man; rather, the judgement of the most suitable surrogate for man must be made independently for each major health effect. Finally, it is noted that although there is some similarity between acute health effect phenomena produced by PCB exposure in the monkey and human Yusho disease, it would be incorrect to equate Yusho disease with PCB intoxication because of the much more complex mixture of compounds encountered in Yusho oil than in a commercial PCB mixture.

Skin and Other Cutaneous Tissues

Commercial PCBs are capable of producing skin lesions in the monkey model and in exposed humans. Chronic administration of PCBs to the monkey produces chloracne. In humans occupationally exposed to PCBs skin disorders including chloracne have occasionally been observed. These skin disorders have been shown to be reversible in some of the animal and human studies.

Liver Effects

PCB mixtures are capable of generating important effects on liver tissue in animal models. These effects include: (a) increase in liver weights; (b) histopathologic changes in liver including enlarged hepatocytes, deposition of fat droplets in tissue, and tissue necrosis and cell death; (c) enlargement of the liver: (d) the occurrence of adenofibrosis, a benign lesion; and (e) an increase in proliferative lesions of the liver, including increases in hyperplastic foci and nodular hyperplasia. These increases in proliferative lesions appear to increase in severity with increasing degree of chlorination of the PCB mixture, as seen in the greater potency of Aroclor 1260 over Aroclor 1254. The effects on

liver tissue are generally reversible at lower doses but trend toward irreversibility with increased dosing.

However, in contrast with the positive findings of PCB effects on liver tissue in animal models, no significant effects on liver function tests have been observed from clinical data on human populations exposed to PCBs in the occupational setting. Further, there has been no epidemiological finding of liver disease in U.S. occupationally-exposed personnel. Also, as noted in the Yusho discussion about persons exposed to contaminated cooking oil with a PCB content of 1000 ppm, there was no finding of liver disease in either jaundice or hepatocellular injury.

Gastric Lesions

When tested in monkeys and rodents, PCBs show species specificity with respect to a toxic effect on the gastric epithelium, or stomach lining. In the monkey, with Aroclor 1242, there is a mucous conversion of the gastric epithelium that can best be described as a dysplastic growth pattern. This growth pattern does not constitute a neoplastic transformation. In rodents, PCBs do not evoke this effect on the gastric mucosa. In humans occupationally exposed to PCBs there are no clinical findings to date of gastric lesions, and no evidence of stomach cancer due to this exposure.

Carcinogenesis: Experimental and Clinical

A sizeable volume of animal experimental work has been directed toward chronic studies in several species: the mouse, the rat and the dog. There are some ar-

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... debate by the inve

...ion of the Category I team the following re

...ons that can be drawn from presently available data: (a) the e

on carcinogenicity is negative for gastrointestinal carcinoma and bladde

cinoma in rats and hepatocellular carcinoma in the dog; (b) some studies

reported an increase in hepatocellular carcinoma in mice and rats expos

commercial PCBs chronically, whereas other studies have afforded negative

sults.

With respect to the possibility of cancer linked to exposure of humans to PCBs epidemiological studies show to date essentially negative results for hepatocellular carcinoma, gastrointestinal carcinoma and all other forms of cancer. There is a single preliminary study that purports to show an increase in melanoma (skin cancer) in occupationally exposed people, but the full data display and analysis have not been made for this study. In contrast, in two larger and more detailed studies, this finding has not been confirmed; no excess incidence of melanoma in exposed personnel has been observed.

Retrospective mortality studies of PCB-exposed human populations have not demonstrated a consistent relationship between extent of exposure and the development of any particular type of cancer. The human studies in hepatocellular carcinoma are not comprehensive, but to the extent that they have been developed the results do not confirm the projection of a risk for liver cancer based on the animal studies. Some findings of increases in lymphatic and hematopoietic malignancies were below the level of statistical significance, and were refuted by observations of changes in the opposite direction in other epidemiological studies. Even findings of statistically significant differences between exposed

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and control populations with respect to the incidence of rectal cancer in women at one plant have not been confirmed by observateions in other studies. The variance in these findings points up the important principle that the Standard Mortality Ration (SMR) may vary widely in different studies, and that undue emphasis should not be placed on the SMR found in one study unless it has been confirmed by similar findings in repeat or parallel studies.

Reproductive Effects

Experimental work with commercial PCB mixtures and animal models has been directed to the reproductive process itself, to teratogenesis in the offspring, and to possible fetotoxicity. In most test species PCBs produce deleterious effects on reproduction at high dosages. In the female monkey at relatively high dosages, difficulties are encountered in conception, in implantation of the fertilized ovum, and in carrying the fetus to term. Similarly dosed, the male monkey does not transmit these difficulties to the reproductive process. In the human, exposed occupationally or otherwise to PCBs, there is in general no evidence for adverse effects on the reproductive process, although there are little data from which to draw conclusions. In the very special case of Yusho exposure to high levels of PCBs and other polychlorinated hydrocarbons, the newborn in significant proportion were pigmented, small, and showed a retarded rate of growth. However, this pigmentation dissappeared and the infants caught up with control population infants in total growth.

The potential for PCB-induced teratogenesis, or production of defects in the embryo or fetus, has been investigated in several species of test animals. Most animal tests have yielded negative results when PCBs were administered to preg-

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...or organogenesis. Sever...

...ment might be noted. In mice, a single ...orachlorobiphenyl, induced a behavioral defect ("waltzing s... that may be related to an anatomical defect in the inner ear. PCBs in ... produce some delay in inplantation. In rats, no gross teratological ... were observed, but some alterations in thyroid structure or function prod... PCB administration might fall under the definition of terata. In dogs a swine, no teratological effects were noted at lower PCB doses; however at highest doses of PCB in the feed, at which the dam suffers marked reduction food consumption and is therefore nutritionally deficient, there a dose-related teratological effects in the offspring. In monkeys dosed wit PCBs, there are no dose-related abnormalities in the offspring, but they are smaller in size. Based on those observations, it is the Category I team's conclusions that commercial PCBs present no appreciable risk of teratogenicity in offspring of human females exposed under occupational conditions.

In test animals, i.e. rats, dogs and rabbits, PCBs are fetotoxic when administered at relatively high doses to the pregnant female. In the human, the only reported epidemiological evidence for fetotoxicity in exposed populations stems from the unique Yusho event, in which causation may not be linked to PCBs.

Mutagenesis

Investigations of possible mutagenesis from acute or chronic exposures to commercial PCBs have shown negative results in a series of in vitro and in vivo test systems. Isolated bacterial test systems (Ames test) and human lymphocytes in culture showed no evidence for PCB-induced mutation or transformation. With in

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vivo systems in intact animals: (a) cytogenetic tests for alterations of cell structures or for induction of chromosome abnormalities yielded negative results; and (b) both the mouse micronucleus test and the dominant lethal test demonstrated negative results. Incubation of human lymphocytes in culture with PCBs caused an alteration in glucose transport through the cell membranes.

There is no significant evidence that PCBs are mutagenic in test systems, and no reports of such activity in human populations. It is quite unlikely that commercial PCB mixtures would exert mutagenic activity in humans. This conclusion is consistent with the lack of excess cancer incidence observed in PCB-exposed human populations.

Other Health Effects

This grouping includes enzyme induction, immunocompetence and porphyria. PCBs induce mixed function oxidases (MFO) in the liver of test animals. The important issue is whether or not this process includes the specific induction of cytochrome P-448 as a general property of the PCBs, with the added implication that some oxidase system is being induced that could be involved in chemical carcinogenesis. Several conclusions were reached with respect to this issue: (a) the predominant effect of commercial PCBs is cytochrome P-450 induction, not P-448; (b) commercial PCBs in the U.S. can contain up to about 2 ppm of PCDFs; and (c) the PCDFs can induce cytochrome P-448. From these observations in animal model systems and our judgment, it is concluded that under conditions of U.S. occupational exposure to PCBs, none of the MFO inducing actions of the commercial mixtures will be of toxicological significance over the lifetime of a PCB-exposed person.

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With respect to potential PCB effects on immunocompetence in test animal systems, some observations are pertinent to the assessment of probable hazard in the human. It has been observed in chicks that if the PCB dosages are high enough, atrophy of the splenic pulp and necrosis of the lymphoid system can be demostrated. Similar indicators of change in immunocompetence can also be produced in ducklings, mice, and monkeys as a consequence of severe change in nutritional status. High doses of PCBs leading to marked reduction of food intake and utilization can lead to such changes in nutritional status. These considerations lead to two general conclusions relative to the PCB-exposed humans: (a) as projected form animal studies, if the PCB dosage is high enough to lead to general toxicity in the human (e.g., decreased food intake, fall in body weight, fall in weight gain), immunosuppression may be demonstrable secondary to malnutrition; and (b) at lower dose levels, there is no likelihood of significant immunosuppression.

Porphyria, or deposition of porphyrin-derived pigments in liver and urine, has been observed in experimental animals such as the rat and rabbit dosed with PCBs. The effect has a delayed onset, and especially in the rat, seems to take place by mechanisms different from those employed by known chemical porphyria-producers in the human. It is concluded that, aside from the unique case of Yusho disease, no evidence has accrued for the occurrence of porphyria in populations exposed to PCBs even under high level occupational exposure conditions.

Epidemiology

This section (XII) of the study presents a separate, independent assessment of

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the recorded epidemiological literature and data bases on human exposures to commercial PCBs, and on the significance of the health effects attributed to these exposures.

Summary points in this assessment include the following: (a) mortality data, based on very small numbers of deaths, do not confirm a carcinogenic effect on PCBs in man; (b) data on human skin lesions in relation to PCB exposures have shown variability in incidence of this effect with geographical locus and with increasing blood level indicators of exposure; (c) data from studies of liver enzymes and liver function suggest changes in one or more enzymes related to PCB exposure that are not associated with liver disease and that occur at levels below those at which chloracne occurs; (d) there is frequently a positive correlation between PCB levels and triglyceride levels in blood; and (e) epidemiological data on reproductive effects, hematology and immunology in humans exposed to PCBs do not suggest abnormalities in these systems or processes.

Human Occupational Exposure Levels

Of the various effects noted in animal test systems, only dermatological effects, including some chloracne, have been clearly demonstrated in human populations at the dosage levels associated with occupational exposures. Table 10 summarizes the nature and intensity of some exposures that have occurred to personnel involved occupationally with PCBs and the biological indices that have accompanied these exposures, measured as PCB content in blood and adipose tissue.

Since the risk to human health from even high level occupational exposures has

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...ant r...

...oup states, "On pp. 1, 2-1, ... and discuss Weisburger's and William's ...ors, and epigenetic and genotoxic mechanisms. H... ...int out that the concept and the classification of carcinoge... and William are not shared by many."

The EPA reviewers may be justified in commenting that the classific... cinogens by Weiseburger and William "is not shared by many" if by many more than a few but most certainly not a majority of cancer researcher view of relevant recent texts available to the authors revealed that ... cluded extensive discussions of promotion and initiation in cancer causatio... literature search via cancerline for 1981 using key words revealed 40 citati... on promotion and hepatic cancer and 58 on initiation and hepatic cancer. EP reviewers should be aware that several of these papers included work presented at EPA sponsored symposia on "Organ and Species Specificity in Chemical Carcinogenesis", March 2-4, 1981 in Raleigh, NC and the "International Symposium on Health Effects of Tumor Promotion", October 12-15, 1981, Cincinnati, OH. In several of these articles PCBs were cited as promoters. Papers of interest discussing PCBs as promoters in these references included authorship by ranking EPA and government scientists Stara and Moore as well as the highly respected researchers Peraino, Williams, Higginson, Newberne, Miller and Miller, Pitot and Allen.

A most effective rebuttal of the EPA reviewers contention is eloquently made by

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quoting from a paper by Dr. Albert Kolbye of the FDA. Dr. Kolbye is a physician, epidemiologist and lawyer and an accomplished Federal regulator of carcinogens. Dr. Kolbye articulated the same philosphy as the authors in his paper "The Application of Fundamentals in Risk Assessment," whichis attached in its entirety. Dr. Kolbye makes several points, and we quote:

1. One meaning of risk assessment concerns usage of various mathematical models to extrapolate.
2. These models represent a very simplistic approach towards data that in reality reflect highly complex biological considerations not easily explained to non-toxicologists and regulators.
3. Many of the models adopt very conservative premises that in effect assume the hypothesis that there is no "safe" exposure to a carcinogenic chemical and that any exposure will be associated with some definable risk for cancer induction in the population at large. This philosophy implies that there are no threshold phenomena associated with cancer induction.
4. The no-threshold hypothesis evolved in relation to various experimental and epidemiological studies concerning the biological hazards related to penetrating ionizing radiation. Penetrating radiation by definition penetrates through tissues without respecting many of the physiological barriers such as membranes which have very important and complex functions to regulate the entry and exit of chemicals in cells and micro-cellular organelles.
5. We should consider the balance between biological damage and biological repair. If normal repair is over-whelmed by excessive damage, cancer and genetic damage are likely to occur, provided the somatic or germinal cells involved survive.
6. If exposing test animals to a chemical is associated with a statistically

significant increase in the incidence of cancers in the test animals as compared to unexposed controls, our present practice is to designate the chemical substance a "carcinogen."

7. Perhaps it is now appropriate to question the validity and sufficiency of that premise.

8. A more fundamental question is whether or not all influences on the incidence of cancer in animals or humans are necessarily related to direct "carcinogenic" action per se (in the sense of electrophilic activity leading to covalent bonding with DNA. Many scientist and regulators concerned with the prevention of cancer are insufficiently aware of a very extensive body of scientific literature which documents the fact that many factors can influence the incidence patterns of cancer in animals and humans.

9. A very substantial body of evidence leads to the conclusion that the induction of cancer is a multistage process.

10. In its simplist form, the progressive events involved with the induction of cancer have been referred to as the "initiation" and "promotion" stages of carcinogenesis.

11. Usually, the first event in this multistage progression takes place when certain types of damage to DNA are caused by viruses, radiation, or chemical insult.

12. The subsequent stage of carcinogenesis has been referred to as the "promotion" stage which has been extensively studied.

13. These phenomena have been reproduced experimentally or have been observed to occur not only in skin cancer, but also with respect to the induction of malignancies in liver, forestomach, lung, breast, kidney, bladder and colon.

14. Promoters will facilitate, enhance, and potentiate the effective potency of the initiators.

15. Direct-acting complete carcinogens have the ability by themselves both to initiate and promote tumor induction.

16. Many potentially carcinogenic chemicals require metabolic activation.

17. Many compounds can enhance or inhibit carcinogenesis without being carcinogenic themselves by inducing or inhibiting microsomal enzymes.

18. Many polycyclic aromatic hydrocarbons have this effect, as do the notable examples of polychlorinated biphenyls and phenobarbital. In many instances, they induce more deactivation than activation, but in some instances they augument activation. These phenomena have been extensively described and documented in the scientific literature.

19. As discussed earlier, other chemicals are capable of inducing a series of changes in the same target cells that are susceptible to initiation of cancer, but these chemicals are only capable of acting as tumor promoters or tumor potentiators. Examples of these chemicals range from the croton oil derivatives, such as certain phorbols, on through a broad spectrum of other naturally-occurring or man-made compounds. Many of these compounds have been designated already as potential carcinogens by observing statistically signifcant increases in the incidence of cancer associated with exposures to these chemicals. It may be of interest to suggest that chloroform and carbon tetrachloride have tumor promoting or potentiating activity, as do saccharin, DDT, PCBs, certain phenols, phenobarbital and, believe it or not, such substances as ethanol, bile acids, citrus oil, and others, including hormones such as estradiol.

20. The term "hyperplastic toxicity" is used in this presentation to describe toxicity-induced cell proliferation associated with increased mitotic activity, increased DNA (as judged by increased density of nuclear chromatin staining or indices of increased DNA synthesis) and other changes associated

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with enzyme and membrane functions which are not of a malignant nature per se.

21. Certain patterns of hyperplastic toxicity appear to be identical and coincidental with certain biological phenomena observed to occur when the classical tumor promoters are administered.

22. If these protective metabolic pathways are functionally distorted or impaired, biological susceptibility to cancer induction can be increased.

23. As mentioned earlier, complete carcinogens can both initiate and promote cancer by themselves, but differences in dose-response have been observed and documented, which suggest that the promoting action of complete carcinogens is related to higher and repeated dosages of the same chemical, whereas initiation of malignant transformation may occur at lower doses. This implies then that the risk for cancer induction by a complete carcinogen will be increased as exposure to that carcinogen increases, because not only will a greater amount of cellular initiation be effected, but the promoting action of the compound will be more effectively expressed by repeated exposures and thus these driving forces will result in the faster induction of cancer.

Our current practice is to dose test animals at substantial levels to determine whether or not a compound induces cancer. If such dosing results in cell damage such as hyperplastic toxicity, which may invoke tumor promoting or potentiating activity, the fact that endogenous initators (such as nitrosamines) exist in the mammalian body implies that a positive induction of cancer in a population of test animals will not differentiate between initiation and promotion. Therefore we will not know from this evidence alone whether the "carcinogen" is an initiator or a promoter, or both. If the

compound when tested at substantial levels can potentiate the effective carcinogen potency of endogenous carcinogens by other mechanisms, or if it acts to decrease biological susceptibility to cancer induction from endogenous carcinogens, or from other carcinogens that may exist environmentally, again we will not be able to tell what category of carcinogenic activity we are dealing with unless we ask the relevant questions in the first place and develop the data to provide relevant answers.

24. We then should consider classifying the induction of cancer into two classes: First Order, those having the capability to induce cancer at subtoxic doses, either because they are effective initiators or complete carcinogens; and Second Order, those that act to influence the induction of cancer by inducing various forms of hyperplastic toxicity by activating endogenous electrophiles, or by decreasing biological resistance to other independently operating patterns of cancer induction.

25. Investigations could be conducted such as using phenobarbital and polychlorinated biphenyls to induce microsomal enzymes and to promote hyperplastic toxicity in organs such as liver in order to determine the effects of added stress.

26. Second Order compounds should not be called "carcinogens", even though under some circumstances and at some doses they may be powerful driving forces that can substantially influence cancer induction.

27. Epidemiological studies can provide much needed information concerning biological susceptibility and resistance factors, particularly in relation to human metabolism, nutrition, and genetic factors which are extremely important.

4. The EPA-HERD reviewers state, "On pp. 1, 2, and 1-5 the authors discuss

the large number of negative carcinogenicity studies for PCBs and present the inadequacies of the positive studies. They do not mention the inadequacies of the negative studies. For example the reference papers show that only a few of the negative studies are sufficient duration to adequately characterized them as negative studies. Most of the studies quoted in the six articles are of one year or less duration (e.g., see article by Crump, p. 24). For the positive studies, they criticize that the length of exposure was too short for an adequate study design (p. 2-3). This is not a relevant concern for a positive study."

"The authors also stated that the positive studies should be discounted because of inadequate design. If this is the case, the negative studies should also be discounted as well. It is far more difficult to prove a negative result than a positive one."

The authors agree with the HERD group that the length of an animal carcinogenicity study is more important for negative than positive results. However, the authors came to the same conclusion as EPA (5) i.e., the length of the studies in rats make the comparisons of these data more relevant (see p.C80-C83 of reference 5). However, the suthors disagree with the EPA's interpretation of the rat studies. The EPA document (5) implies that the NCI bioassay was inadequately designed because it lacked the large number of animals used by the Kimbrough study. The other rat studies represent negative data. For the EPA document (5) to suggest that study population size is the reason that a statistically insignificant number of hepatocellular carcinomas was seen is not true. The authors disagree with EPA and conclude as did NCI and its review group that the NCI study, while not optimal, was of sufficient size. The Kimbrough study reported a 78% incidence for neoplastic nodules and a 14% incidence for hepatocellular

carcinoma. The Levinskas paper, which was part of our review, shows that in the 100 animals exposed to 100 ppm PCBs (adding the Levinskas and NCI results for Aroclors 1260 and 1254) that no neoplastic nodules were reported and only a 2% rate for hepatocellular carcinoma was seen. It seems obvious to the authors that the Kimbrough study in a vacuum does not agree with the rest of the rat data, and that this disagreement is not due to study number, study duration, or statistics, but is caused because different rates of cancer were reported. (Note: papers by Mantel provide techniques for combining tumors data for extrapolation purposes.)

The EPA also suggests that the larger population size is a criteria for choosing Kimbrough's study over the others (see page C-80 thru C-83). We feel it is inappropriate and biased to ignore the negative data and the implications it has upon the carcinogenic potential of PCBs. Moreover, if one applies the EPA's line of reasoning to the human studies of Bahn et al. (6) and Bertazzi et al. (6) they are of such a small size compared to that Brown and Jones (3), that one would conclude that the Brown and Jones study is the only acceptable study. This dubious line of reasoning would leave the EPA with no significant increases in human mortality from any cause.

5. The EPA-HERD reviewers state, "Often, observations cited in the review papers are neglected or omitted in the CMA Summary. For example, p. 3, paragraph 2, sentence 3 of Summary: "The preponderance of studies has not identified a clinical disease associated with exposure to PCB, nor has it provided persuasive evidence of health impairment" compared to Paper No. 1, p. 22, paragraph 1, last sentence: "...a single study which suggests that diastolic blood pressure may be related to blood levels of PCBs." This study suggests some

cardiovascular toxicity. In addition, dermatologic reactions is known to be associated with PCBs poisoning."

The authors agree that PCBs are known to cause chloracne and other dermatologic reactions. The authors had previously stated clearly that acne and dermatitis are undesirable symptoms of chemical exposure. The authors are aware of no evidence or claims that these symptoms represent a classical disease state or seriously impaired health. The reference in paper 1 of our review to the Kreiss et al. study (6) suggesting an increase in blood pressure is taken out of context by the HERD reviewers for it is contradicted by a similar study which found no such relationship (see paper #1, page 16, first paragraph). Furthermore, the authors feel that the Kreiss study is not "suggestive evidence of some cardiovascular toxicity" as concluded by the HERD group. We do not understand why Kreiss et al. failed to show what the changes in blood pressure were. The magnitude of the change is at least as important if not more for others to know than is the statistical difference. Since absolute changes were not provided it is impossible to comment by other than speculation. Likewise, although log DDT levels were not significantly correlated to changes in blood pressure the strong correlation between blood levels of DDT and PCBs undermines the significance of any finding attributed solely to PCBs. The data presented by Kreiss et al. sugggests that the strongest relationship they found was between serum levels of PCBs and DDT. Thus, for diastolic blood pressure to be statistically related only to PCBs and not the higher serum levels of DDT suggests that the relationship is either tenuous and weak or that it is a statistical fluke of this particular data set. The fact that Bumgarner found no relationship further substantiates this line of reasoning. Lastly, ~~the~~ Kreiss et al. themselves state on page 2509 (J.A.M.A., volume 245) that "In the absence of a control group, the explanation for the ex-

cess prevalence of hypertension among triana residents is debatable."

6. The EPA-HERD reviewers state, "The Summary contains too much emphasis on the possible carcinogenicity of PCBs and does not mention much on the possible chronic health effects. The six articles have more details of the chronic effects."

6. The authors do not feel that the summary overemphasizes the possible carcinogenicity data. The EPA's own document likewise considered cancer as the most important issue and concern associated with PCB exposure, therefore, it is not surprising to find that the authors placed special emphasis on this health effect. As for the other potential chronic effects each was discussed. While the authors agree that the animal data has identified certain potential hazards the negative data suggest that these potential hazards are not consistent nor potent responses in avery species. Furthermore, the authors concede that while one might speculate that large doses of PCBs may cause various detrimental effects in humans, the authors point out that the highest exposure group, capacitor workers, appears to have been exposed at levels below those that would cause these serious adverse effects in humans. Thus, the authors continue to maintain that current exposures to PCBs, which are much lower than previous occupational exposures, do not appear to be associated with an identifiable hazard, and so the risk from the existing environment seems to be minimal or insignificant. The authors consider it prudent to suggest that a 1000-fold reduction in exposure is a sufficient margin of safety for the threshold effects that have been identified, in humans e.g., skin disorders and induction of liver enzymes.

7. The EPA-HERD reviewers state, "One of the controversial issues in this do-

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cument is that the CMA contractor feels that PCBs are tumor promoters and not initiators. Since promoters may have threshold and reversible effects, the authors feel that low level exposures do not represent a hazard for cancer. The evidence for this assertion is presented on page 2-7 through 2-8 and again on pages 3-17 through 3-19. These arguments can be summarized as follows."

1) PCBs increase the frequency of liver tumors in rodents; a tumor type which occurs spontaneously in these animals.

2) PCB induced tumors are not metastatic.

3) PCB tumors are not transplantable.

4) Promoters are not mutagens. Many of the mutagenicity test on PCBs were negative.

5) Continued presence of PCBs is required to sustain liver neoplasia and removal may cause tumor regression.

We do not understand the EPA's line of reasoning concerning whether or not carcinogens may be labelled initiators or promoters. Regardless of the terms used to describe chemical carcinogens, e.g., promoter, epigenetic, initiator, oncogens etc., the scientific literature is clear, there are vast differences in the mechanisms by which chemicals may increase the rate of cancer in animals or humans. The authors document clearly points out that while regulatory agencies hav not yet addressed this issue, it is no longer valid to mathematically model the human cancer risk as if the chemical were a true, initiating carcinogen for

which there are no threshold doses, merely because it increased the number of tumors in an animal species. This discussion was presented in rebuttal #3 (page 27 of this report). The scientific literature clearly shows that chemicals may increase cancer by a variety of effects that have thresholds (e.g. recurrent injury, enzyme induction, immunosuppression, hormonal etc.) In fact, the example used by EPA-HERD concerning a DNA change as a result of chemical effects on DNA methylase would obviously classify it as a threshold toxicity. The authors points are two fold. First, for those potential "carcinogens" which act via mechanisms having thresholds it is incorrect for the EPA to model the risk based upon nonthreshold assumptions. Second, there is sufficient evidence for PCBs to conclude that they are not initating carcinogens. When one considers the known promotional pressures that enzyme inducing, hepatotoxic agents such as PCBs can exert on the spontaneous incidence of liver cancer if anything it is probably more surprising that several of the rat studies were negative.

8. The EPA-HERD reviewers state, "There are several problems with this line of reasoning. First the mechanisms of action of initiators and promoters are becoming less clear. The dogma that initiators cause mutations and promotors have "epigenetic" effects in cancer expression is no longer totally accepted. Cairns has recently proposed that initiators may not act through the induction of mutations by way of DNA damage as is usually thought. Further, the term epigenetic is not very useful; for example, what if a chemical caused a heritable change in chromatin structure by altering the action of DNA methylases. This affects the DNA and therefore is "genetic" and yet neither the sequence of bases nor the number of chromosomes is affected. Because of such difficulties it is better, perhaps, not to sterotype chemicals.

Even if we accept the contractors reasoning, it is important to note that not all mutagenicity tests on PCBs were negative. In the Monsanto document entitled "A review and evaluation of carcinogenicity in mice and rats and mutagenicity studies with PCB" several positive mutagenicity tests were cited along with the negative results: Aroclor 1221 and 4-chlorobiphenyl were positive in the Ames test. TCB and the 3, 4 epoxide of TCB induced single strand breaks in DNA of L-929 cells Kanechilor 300 was found to induce chromosomal aberrations in vitro while Kanechlor 500 was positive in vivo. Continuous exposure of C3H 10T 1/2 cells to Arocior 1254 caused cell transformation to type III foci. These cells formed a sarcoma when implanted into hexachlorobiphenyl also caused an increase in unscheduled DNA synthesis in CHO cells while Aroclor 1254 induced chromosome damage in ring doves fed a 10 ppm diet. Clearly, based on these data one can argue that PCBs may have initiator activity."

The authors strongly disagree with the EPA-HERD groups assessment that these in vitro tests could be used to argue that PCBs may have initiator activity. On the basis of sedimentatiom rates, Stadnicki et al. (7) reported that the epoxide of tetrachlorobiphenyl caused single-stranded chromosomal breaks in the DNA of L-929 cells at concentrations ranging from 1 µg/ml to 100 µg/ml. A mixture of two hydroxy metabolites, and to a lesser extent tetrachlorobiphenyl, caused some damage at 20 µg/ml and significant damage at 100 µg/ml. The significance of this test at these high in vitro concentrations is questionable

Using Drosopholia melanogaster and Bombyx mori as the eukaryote test species, neither the French PCB mixtures, Clophen 30 and Clophen 50, or the Japanese mixtures, Kanechlor 300 and 500, were mutagenic. Odashima (5, 7) studied chromosomal aberrations in Yoshida sarcoma cells at PCB concentrations causing 50%

growth inhibition: Kanechlor 300 gave a positive response and Kanechlor 500 a negative one. Odashima also reported cytogenetic analysis of bone marrow cells in mice exposed to PCBs at a near lethal dose. This test gave paradoxical results considering the previous test. Odashima listed exposure to Kanechlor 500 as positive and exposure to Kanechlor 300 as negative.

Norback et al. (7) did report that Aroclor 1254 transformed C3H10T1l/2 cells to Type III foci after six weeks of continuous exposure to 10 μ/mL of Aroclor 1254, while a concentration of 1 μ/mL was negative. However, Norback and co-workers concluded that this effect of PCBs in culture suggested promotional activity rather than an indicating effect. In contrast to this study, Pienta reported Aroclor 1254 as negative in the Syrian hamster cell transformation test (7).

Peakall (7) reported chromosomal aberrations in doves fed a 10-ppm diet of PCBs. The frequency changed from 0.8% in controls to 1.8% in treated birds. The average rate of chromosomal aberrations among treated eggs was higher than the highest control value in only 4 of 17 pretreated embryos. In contrast, PCBs injected into white Leghorn eggs up to concentrations of 20 ppm, while toxic, were not clastogenic.

A thorough review of all mutagenicity tests reveals that PCBs gave primarily negative responses. While some positive results were reported, these were largely in vitro tests and for the Kanechlor brands, which gave inconsistent and mixed results for the 300 and 500 brand mixtures. The relevance of some of the in vitro tests that found positive scores only at concentrations of 10 μ/mL or greater (very high and unlikely in vivo concentrations) is questionable. This interpretation is supported by the fact that in many cases a similar experiment

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gave correspondingly opposite, i.e., negative, results. According to Levinskas (7), "considering the large number of tests conducted, it is not surprising that an occassional suspicious positive finding resulted, simply on a statistical basis". A comparison of the number of Ames tests unable to reproduce the results of Wyndham et al. supports his contention.

It was the consensus of the authors that PCBs do not represent a significant mutagenic risk to humans: these few test that reported positive findings, even counting the contradictory or inconsistent results, do not outweigh the preponderance of negative data in test of far greater relevance. Weisburger and Williams (8) have recently addressed the use of short term testing as a screen to carcinogenicity testing and to determine initiator - vs - epigenetic mechanisms. The mutagenicity tests used include: bacterial mutagenesis, mammalian mutagenesis, DNA repair, chromosome tests, and cell transformation. Using this battery of tests PCBs, as we concluded, represent an insignificant mutagenic risk in humans.

Lastly, the authors do not find the test or methods utilized in the Stadnicki or Peakall studies are among those tests considered by and promoted by the EPA a s useful criteria for determining mutagenic activity. One does find, however, that the dominant lethal, Ames Assay, cytogenetic analysis, the eukaryote tests using Drosophila melanogaster, cell transformation, and unscheduled DNA repair tests are tests which have been promoted by the EPA and others as useful criteria for establishing mutagenic activity. PCBs are negative, and overwhelmingly so in these test systems.

9. The EPA-HERD reviewers state, "Finally, in calculating the risk estimate for

increased human cancer cases caused by exposure to PCBs, the contractor made (but did not state) an enormous assumption. It was assumed that because hepatomas were induced in rodents, this was the only tumor type for which humans were at risk. Although the correlation between carcinogenicity in animals and man is good, the issue of site concordance is not clear. Therefore, humans may be at risk for other types of tumors as well. Since the incidence of hepatomas in the human population is low, the risk estimate produces a very low number of PCB induced cancer. However, if these chemicals were also associated with lung carcinoma, for example, risk estimates would be much higher."

The EPA's conclusions regarding what assumptions the authors made regarding human cancer risks are incorrect. Although animal data often indicates the susceptible human it is well known that such is not always the case. However, Crump and Masterman previously suggested human hepatocellular carcinoma (see page 38, 4th paragraph of paper No. 6 in our summary document.) Independent of which cancer site EPA would propose, our contentions stand. The EPA human cancer risk for 1/100,000 lies at 0.8 ng/l or even 80 ng/day can easily be shown to be an unrealistic and indefensible level by a simple linear extrapolation to those doses which would then be expected to produce high cancer rates in humans. In fact, as the authors have stated before the level would have to be several orders of magnitude higher (see answer #1, pg. 13-14).

10. The EPA-HERD reviewers state, "The latter part of the Summary consists mostly of a complete refutation of the risk assessment done by Crump and Masterman, the last document on the "Assessment of Carcinogenic Risks from PCBs in Food, with very little documentation of the reasons for not accepting Dr. Crump's assessment. In his assessment, certain models are used to derive vir-

tually safe doses of PCBs at specified risks. He includes the probit model, the one-hit model, and the multi-stage model. He also uses the one-hit model, and multi-hit models to derive estimates of life time extra risks to humans for certain subpopulations at risk. Although the "Summary" is interesting reading, in most cases it is not of sufficient scientific validity to warrant a response. In any case, the Summary conclusions for risk assessment are not supported by the technical review documents. In fact, unlike the other section such as epidemiology, the risk assessment section does not even attempt to summarize the material in the risk assessment technical document. There are several specific problems with the Summary."

This is simply not true. The authors provided more than sufficient documentation for not accepting Crump's assessment, using several approaches we previously demonstrated that it clearly overestimates the cancer risk in humans when compared to the human data (see pgs. 2-12 of this report). We have also provided an additional and simpler method for demonstrating that the EPA overestimates the risk (see pgs. 13-14 of this report).

The authors agree that the EPA reviewers detected an unfortunate typographical error in the document. This error has been corrected. It should be stressed however that the correct values were used in all calculations.

Several places in the Summary (pages 4-5 and 1-3) the authors conclude that there is little reproductive risk from PCBs in animals. The Crump and Masterman document contains the data from the reproductive studies in monkeys which showed effects at levels as low as 2.5 ppm. The PCB data is unusual in showing reproductive effects at levels lower than those at which carcinogenic effects are

seen. The fact that this is not even mentioned in the summary document, even though one of their own technical review documents include the data, casts some suspicion in the summary document.

The EPA-HERD group continually confuses risk with hazard. Risk is defined as the probability that an adverse effect will occur. Hazards are those toxic responses that can be induced at clearly toxic doses. It is true that the monkey and mink studies have reported reproductive problems not seen in other species. However, reproductive dysfunction caued by a chemical at doses which are clearly toxic and lethal to the mother, fetus and newborn is not a relevant finding when one is exposed to doses which are orders of magnitude lower than the toxic, lethal levels. The research by Allen and coworkers (9-12) clearly demonstrated that female monkeys were severly chemically intoxicated at 25 ppm PCB after two months of exposure by which time one of the six had died. After many months of a 2.5 ppm or 5 ppm exposure again the females were clearly intoxicated and suffered many adverse physiologic changes. The newborns were clearly sick and 50% expired within 8 months of birth which was ascribed to PCB poisoning. At fatal doses, many chemicals produce reproductive disorders, but it cannot be concluded that such a finding represents an unusual risk at nontoxic doses. Environmental exposure to PCBs are low and should not represent a significant reproductive risk. This statement has been substantiated by the study of Kreiss et al. included in paper number 1 of our summary document.

Aside from the biological arguments regarding mechanism of cancer which are used to refute Crump's risk assessment, there is another major argument proposed. It is that if the risks are as large as Crump's estimates indicate, these risks would have been detected by now in high risk populations. The review of

the epidemiology studies show the highest number of cohort deaths studied for sufficient latency periods is less than 100. It is doubtful that relative risks of less than 15-20 times would be detected with this size population (we are presently doing the calculation).

Crump's risk assessment does not agree even with the cohort used in Brown and Jones (3) for it predicts a far higher risk for occupational exposures than they observed.

Using the EPA Water Criteria documents, the authors in the summary section calculated the expected increase over background cancer for certain subpopulations. There is a mistake somewhere in the conversion figure given in Table 3-5 equating 79 ng/1 to 80 µg/day. The 80 µg/day does not produce the expected increases over background shown in Table 3-6. A conversion to 80 ng/day rather than 80 µg/day would produce the estimates shown in Table 3-6 and on pages 4-10 the figure is given as 80 ng/day.

The 80 µg/day is a typing error. The calculations are correctly based upon a dosage of 80 ng/day of PCBs.

On pages 4-6, the authors use the CAG documents which show that if PCBs are not carcinogenic, the allowable daily intake would be 210 µg of PCBs per day. This is calculated using reproductive data in minks (which was similar to reproductive data in monkeys) and a safety factor of 100. This allowable daily intake of 210 µg/day is not disputed by the authors, yet the exposures shown in the table on page 4-11 for capacitor workers is 4 times higher than this allowable daily intake. Therefore, even without considering carcinogenicity, the allow-

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able daily intake of 210 µg/day, which is used by the authors to question the much lower safe levels from cancer data, is already 4 times lower than average exposure of capacitor workers. All the arguments used in the Summary for negating certain models used for extrapolation of cancer sisks by mechanistic arguments would have no relevance to reproductive data.

The authors did not choose to address the 210 µg/day level proposed, which was based on reproductive effects, for two reasons. First, the EPA accepted and uses their cancer risk data (see Federal Register 11/28/80, volume 45 page >9339). Second, the authors stated clearly that the environmental exposures carry no significant reproductive risk. This statement agrees with the EPA estimate of a LOEL level of reproductive problems at 210 µg/day PCB. The usual environmental exposure and current occupational exposure to PCBs is in the microgram per day range (13, 14) this is far below the EPA's level of 210 µg/day. Whether or not the EPA's extrapolation, based on animal data, is accurate for the occupational or any PCB exposures is pure conjecture on the part of EPA. While no one knows at what human exposure, if any, significant human reproductive problems might occur there is no evidence to suggest occupational exposures in the past led to problems in these people.

The authors of the summary document makes no attempt to estimate any risks according to their proposed model of cancer. This may be because the probit model, also used by Crump, gives the lowest risks of almost any model available at low levels. The safe levels shown on page 34 of Crump's report using this model are below the exposure of average capacitor workers, even for risks as high as 10^{-4}.

The authors proposed no specific model for cancer, we simply stated the techniques used by the EPA were far too conservative, were based incorrectly on the assumption that PCBs are initiators and that concluding that PCBs represents a significant carcinogenic risk is a conclusion with which we do not concur, and feel cannot be substantiated.

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